Manganese Superoxide Dismutase and Catalase Are Coordinately Expressed in the Alveolar Region in Chronic Interstitial Pneumonias and Granulomatous Diseases of the Lung

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Free radicals have been suggested to play an important role in the pathogenesis of interstitial lung diseases, the most important of which are chronic interstitial pneumonias such as usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia (DIP) and granulomatous lung diseases such as sarcoidosis. Because manganese superoxide dismutase (MnSOD) and catalase are two important intracellular antioxidant enzymes that probably play a central role in lung defense, the localization and intensity of these two enzymes were assessed by immunohistochemistry in biopsies of UIP (n = 9), DIP (n = 11), pulmonary sarcoidosis (n = 14), and extrinsic allergic alveolitis (n = 6). The mRNA of these enzymes in selected samples of bronchoalveolar lavage was assessed by Northern blotting. Catalase, but not MnSOD, was constitutively expressed, especially in type II pneumocytes of the healthy lung of nonsmoking individuals. In contrast, manganese SOD immunoreactivity was markedly upregulated in all of the interstitial lung diseases investigated, whereas no increased expression of catalase could be detected in any case. Both enzymes were expressed, especially in type II pneumocytes and alveolar macrophages of DIP and UIP, in the well-preserved areas of the lung, in the acute fibromyxoid lesions of UIP, and in the granulomas of sarcoidosis and extrinsic allergic alveolitis. The simultaneous expression of MnSOD and catalase in the alveolar region suggests their protective role against the progression of lung disease. **Lakari E, Pääkkö P, Pietarinen-Runtti P, Kinnula VL. Manganese superoxide dismutase and catalase are coordinately expressed in the alveolar region in chronic interstitial pneumonias and granulomatous diseases of the lung.**

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Although free radicals have been suggested to play a role in a variety of interstitial lung diseases, there are few, if any, studies available on human lung.

Granulomatous diseases of the lung, such as sarcoidosis, are characterized by infiltration of multiple cells, such as $CD4^+$ lymphocytes, macrophages, and monocytes, to the lung (1). The activation of inflammatory cells leads to a generation of reactive oxygen species (2), which may also play an important role in the pathogenesis of these diseases. A study carried out in our laboratory also revealed elevated expression of manganese superoxide dismutase (MnSOD), one of the most important superoxide radical-scavenging antioxidant enzymes, in the granulomas and alveolar type II pneumocytes of pulmonary sarcoidosis and extrinsic allergic alveolitis (3).

Idiopathic pulmonary fibrosis (IPF) represents the clinical manifestation of usual interstitial pneumonia (UIP) or desquamative interstitial pneumonia (DIP) in most cases. On the basis of histopathological classification, the other uncommon manifestations of IPF are nonspecific interstitial pneumonia (NSIP) and acute interstitial pneumonia (AIP, Hamman Rich) (4). The most important findings in UIP include the appearance of patchy, nonuniform foci characterized by the accumulation of fibroblasts and myofibroblasts forming loose fibromyxoid lesions within the damaged alveolar region with scanty inflammation, and hypertrophy of alveolar type II pneumocytes in the preserved lung (4). On the other hand, the most striking histological finding in DIP is the presence of inflammatory cells, such as macrophages, with uniform cellularity, lack of significant fibrosis, and well-preserved alveolar architecture. Earlier studies of hyperoxic lung injury in experimental animals have yielded histopathological findings similar to those observed in pulmonary fibrosis, i.e., destruction of alveolar endothelium and type I pneumocytes, proliferation of type II pneumocytes, and development of pulmonary fibrosis (5). Previous studies have also revealed oxidant-related lung injury and induction of antioxidant enzymes, most importantly MnSOD, by hyperoxia *in vivo* (6, 7).

A few studies of MnSOD in human lung are available (3, 8, 9), as are several studies of this enzyme in experimental animals (6, 7, 10). Manganese SOD is a mitochondrial enzyme, localized mainly to type II pneumocytes and alveolar macrophages in human, rat, and rabbit lung (11). The expression of MnSOD ap-

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TABLE 1

CLINICAL INFORMATION ON PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA AND DESQUAMATIVE INTERSTITIAL PNEUMONIA

Patient No.	Sex	Age (yr)	Smoking
	UIP		
1	F	66	No
2*	F	63	Ex†
3	M	43	Yes
4	F	48	No
5*	F	58	No
6*	F	43	No
7	F	66	No
8*	F	57	No
9	M	59	Yes
	DIP		
1	M	29	Yes
2	F	43	Yes
3	M	49	Yes
4	F	45	Yes
5	F	42	No
6*	M	47	Yes
7	F	52	Yes
8	F	58	Yes
9	M	43	Yes
10	M	58	Yes
11	F	56	No

* Patients 2, 5, 6, and 8 in the UIP group and patient 6 in the DIP group received oral corticosteroids before the biopsy.
† Patient 2 is an ex-smoker, but the exact date of cessation is not known.

TABLE 2

CLINICAL INFORMATION ON PATIENTS WITH SARCOIDOSIS AND EXTRINSIC ALLERGIC ALVEOLITIS

Patient No.	Sex	Age (yr)	Smoking
	Sarcoidosis		
1*	F	52	No
2	M	45	Yes
3	M	58	No
4†	F	35	No
5	F	57	No
6*	F	55	No
7†	F	44	No
8	F	69	No
9	F	44	No
10	M	27	Yes
11	M	37	No
12	M	34	Yes
13	F	54	No
14	F	26	No
	Extrinsic allergic alveolitis		
1	F	60	No
2†	F	56	No
3*	F	52	No
4†	F	59	No
5	M	64	Ex
6*	F	47	Ex

Definition of abbreviation: Ex = patient had stopped smoking at least 6 mo before the biopsy.
* Patients 1 and 6 in the sarcoidosis group and patients 3 and 6 in the extrinsic allergic alveolitis group received oral corticosteroids before the biopsy.
† Patients 4 and 7 in the sarcoidosis group and patients 2 and 4 in the extrinsic allergic alveolitis group received inhaled corticosteroids before the biopsy.

pears to be low in healthy lung, and it is induced by changes in the cellular redox state and inflammatory cytokines *in vitro* (12–16) and by high oxygen tension at least *in vivo* (6, 7, 17). Manganese SOD has been suggested to be responsible for oxygen tolerance during repeated exposures to hyperoxia and mainly responsible for the protection of various cells against oxidants (18). With the exception of our study on MnSOD in pulmonary sarcoidosis and extrinsic allergic alveolitis (3), no other studies have been conducted on MnSOD in nonmalignant parenchymal lung diseases.

Catalase is localized in peroxisomes, but possibly also in other cell compartments (11, 19), and is detectable especially in alveolar type II pneumocytes and macrophages (11). Catalase is the most important antioxidant enzyme consuming exogenous H_2O_2 in rat type II pneumocytes (20–22). Experimental models and cell cultures have shown no or marginal induction of catalase in response to hyperoxia or inflammatory cytokines (reviewed in references 11, 23, and 24). No systematic studies are available on catalase in human lung diseases.

We investigated the expression of MnSOD and catalase in biopsies of healthy human lung, in chronic interstitial pneumonia such as UIP and DIP, and in granulomatous diseases such as pulmonary sarcoidosis and extrinsic allergic alveolitis. These diseases were selected because they represent different types of well-characterized parenchymal lung disorders. Free radicals may play an important role in the pathogenesis of all these diseases. In this study, the expression of MnSOD and catalase was assessed semiquantitatively in various cell types of the lung in all these diseases and by Northern blotting in samples of bronchoalveolar lavage (BAL) of healthy lung.

METHODS

Patients and Handling of the Specimens

Histopathologically typical cases of UIP, DIP, sarcoidosis, and extrinsic allergic bronchioloalveolitis (i.e., farmer's lung) were retrieved from the files of the Department of Pathology, Oulu University Hospital (Oulu, Finland). The diagnoses were based on light microscopy evaluation, using the histologic criteria presented by Dail and Hammar (25). The biopsies were taken between 1981 and 1998. The clinical patient data were obtained from the patient records of the University Hospital and the nearby Päivärinne Hospital (Tables 1 and 2). Diagnostic lung biopsies were obtained owing to parenchymal involvement. Biopsies were obtained from different parts of the left or right lung. The biopsy material was fixed in 10% formalin under vacuum, to expand the tissue and to remove air bubbles, or perfused by injecting fixative into the bronchioles with a small syringe, as described by Dail and Hammar (25). The specimens were then dehydrated and embedded in paraffin.

The uninvolved peripheral lung tissue, which was used as a control, was obtained from five nonsmokers operated on for a malignant lung tumor or a bronchial carcinoid tumor. None of the control subjects had received corticosteroid treatment before the biopsy, and their lung function parameters were normal. In additional experiments, BAL samples (representing > 90% alveolar macrophages) of

TABLE 3

SCORING THE INTENSITY OF MnSOD AND CAT IMMUNOREACTIVITY IN THE LUNGS OF CONTROL PATIENTS*

Patient No.	MnSOD/CAT		
	Type II Pneumocytes	Alveolar Macrophages	Bronchial Epithelial Cells
1	−/++	−/+	−/+
2	−/++	−/+	−/+
3	−/+++	−/+	−/+
4	−/++	−/+	−/+†
5	−/++	−/+	‡/‡

* Key to scoring: − = negative; + = weak immunoreactivity; ++ = moderate immunoreactivity; +++ = intense immunoreactivity.
† Smooth muscle cells were weakly positive.
‡ No bronchial structures present.

Figure 1. Manganese superoxide dismutase and catalase expression in the alveolar region of normal lung. (*A*) No expression of MnSOD was found in normal lung. (*B*) CAT is strongly expressed in type II pneumocytes (*arrows*). Original magnification: (*A* and *B*) ×210.

selected healthy controls were collected in 4 M thiocyanate buffer and frozen immediately at −80° C.

Immunohistochemistry

Sections 4 μm thick were deparaffinized in xylene and rehydrated in graded ethanol. Endogenous peroxidase was consumed by incubating the sections in 30% hydrogen peroxide in absolute methanol for 10 min. The polyclonal antibodies for MnSOD and catalase (CAT) were a gift from J. D. Crapo (National Jewish Medical and Research Center, Denver, CO) (9). The sections were incubated with the primary antibodies (anti-MnSOD at a dilution of 1:1,000 and anti-CAT at a dilution of 1:200) at room temperature for 1 h for MnSOD and for 30 min for CAT, followed by the biotinylated secondary antibody and peroxidase-conjugated streptavidin included in the Histostain-PLUS kit (Zymed Laboratories, South San Francisco, CA). These dilutions of the antibodies were selected after conducting preliminary experiments with several dilutions between 1:100 and 1:10,000 for MnSOD and between 1:100 and 1:1,000 for CAT. A case showing strong MnSOD and CAT expression was used as a positive control in repeated experiments. The color was developed with aminoethyl carbazole substrate solution (Zymed Laboratories). The sections were counterstained with a light hematoxylin stain. The negative controls consisted of phosphate-buffered saline (PBS) at pH 7.2 and normal rabbit serum for the primary antibodies.

Light Microscopy Evaluation

For immunohistochemical stainings, the whole tissue section was evaluated by light microscopy. At least two sections were evaluated from each biopsy. The results were assessed semiquantitatively by grading the staining intensity as follows: − = negative, + = weak, ++ = moderate, and +++ = intense immunoreactivity.

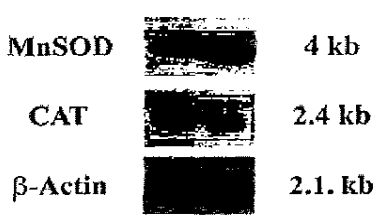

Figure 2. Northern blotting of MnSOD and CAT, conducted on the BAL fluid of unaffected controls, indicates that both enzymes are detectable in healthy lung.

Northern Blotting

Total RNA was extracted from cells suspended in 4 M thiocyanate buffer, using the acid phenol–chloroform method (26). RNA (10 μg/lane for both MnSOD and CAT) was electrophoresed on a 1% agarose gel containing 0.36 M formaldehyde. The samples were capillary transferred onto Hybond-N nylon filters (Amersham International, Amersham, UK) and cross-linked to the filters by UV illumination (UV Stratalinker 1800; Stratagene, La Jolla, CA). Prehybridization was carried out at 58.5° C for > 1 h in a buffer containing 50% deionized formamide, 5× SSC (1× SSC is 0.15 M NaCl plus 0.015 M so-

TABLE 4

SCORING THE INTENSITY OF MnSOD AND CAT IMMUNOREACTIVITY IN USUAL INTERSTITIAL PNEUMONIA AND DESQUAMATIVE INTERSTITIAL PNEUMONIA*

	MnSOD/CAT			
Patient No.	Type II Pneumocytes	Alveolar Macrophages	Bronchial Epithelial Cells	Fibromyxoid Lesions
	UIP			
1	++/++	++/+	+/++	++/++
2	+++/++	++/+	++/+	†/†
3	++/+++	+++/++	+/+	++/++
4	++/++	+++/+	+/++	+/+
5	+/++	++/+	−/+	−/+
6	+/++	++/+	−/−	+/−
7	+/+	++/+	+/+	+/+
8	++/+	+++/+	+/+	+/+
9	++/−	++/−	+/−	+/+
	DIP			
1	++/++	+++/++	++/+	
2	++/+++	+/++	+/+	
3	+++/+++	++/+	+/+	
4	+/++	++/++	+/++	
5	+++/++	++/+	†/†	
6	++/+	+/++	+/++	
7	+/++	++/+	++/+	
8	−/−	++/+	†/+	
9	++/+++	++/++	−/−	
10	−/+	+/−	−/−	
11	+/−	+/+	+/−	

* Key to scoring: − = negative; + = weak immunoreactivity; ++ = moderate immunoreactivity; +++ = intense immunoreactivity.
† No fibromyxoid lesions present.
‡ No bronchial structures present.

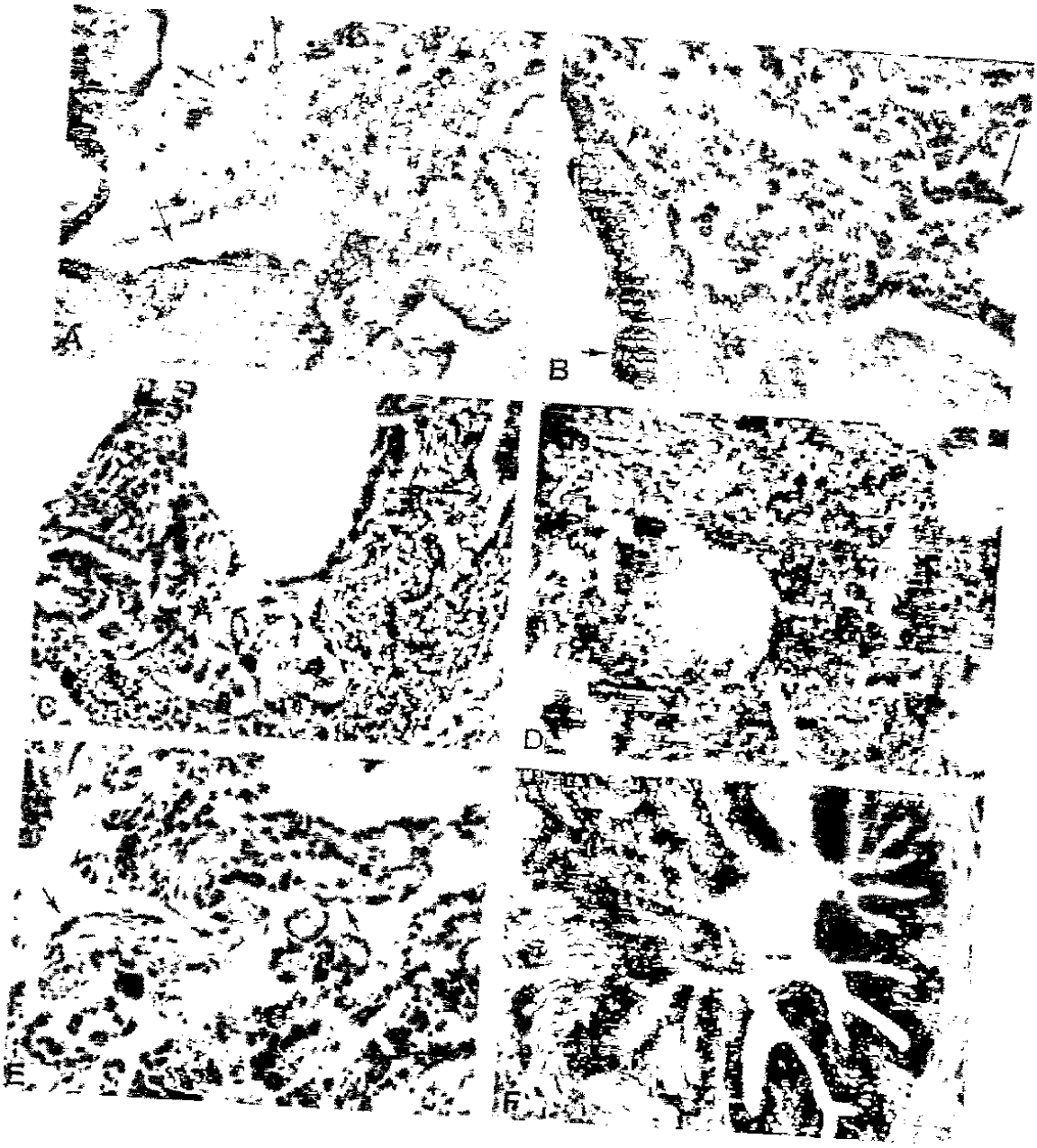

Figure 3.

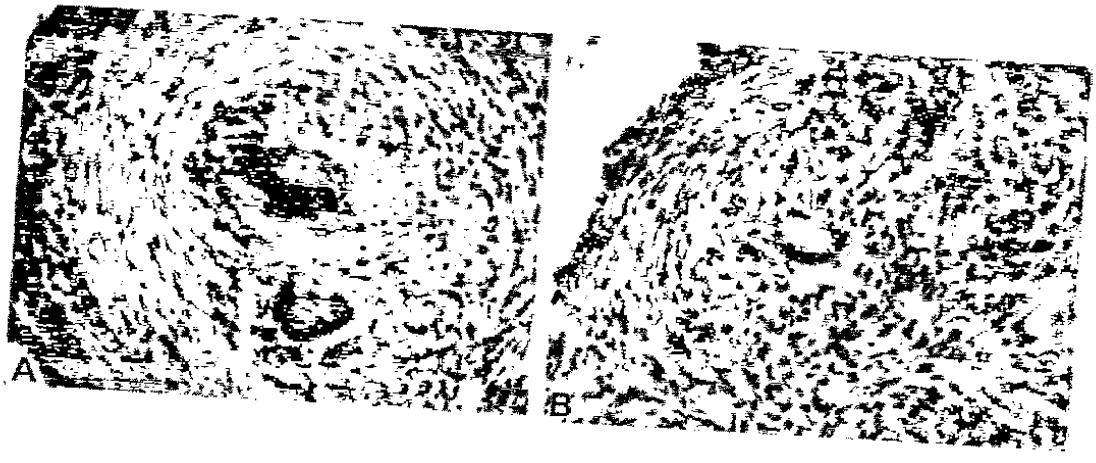

Figure 4.

TABLE 5

SCORING THE INTENSITY OF MnSOD AND CAT IMMUNOREACTIVITY IN GRANULOMAS AND CAT IMMUNOREACTIVITY IN TYPE II PNEUMOCYTES, ALVEOLAR MACROPHAGES, AND BRONCHIAL EPITHELIAL CELLS OF LUNG BIOPSIES SHOWING SARCOIDOSIS AND EXTRINSIC ALLERGIC ALVEOLITIS*

Patient No.	Granulomas MnSOD/CAT	Type II Pneumocytes	Alveolar Macrophages	Bronchial Epithelial Cells
		Sarcoidosis		
1	+++/+	++	+	+
2	/+	+	−	−
3	/−	+	−	−
4	+++/−	++	−	++
5	/+	++	+	−
6	/+	+++	−	+
7	/+	++	+	+
8	/+	++	+	+
9	/+	+	−	−
10	++/+	++	−	+
11	+++/+	++	−	+
12	/−	+	−	−
13	/+	−	+	−
14	/+	+	−	−
		Extrinsic allergic alveolitis		
1	/−	++	−	−
2	/+	+	+	+
3	/+	+	+	+
4	/−†	+	−	−
5	/+	−	−	−
6	/+	+	+	−

* Key to scoring: − = negative; + = weak immunoreactivity; ++ = moderate immunoreactivity; +++ = intense immunoreactivity.
† Only giant cells were present, and they were negative.

dium citrate), 50 mM sodium phosphate (pH 6.5), 5× Denhardt's reagent, and herring sperm DNA (100 μg/ml). ^{32}P-labeled cRNA probes were transcribed from cDNA clones representing nucleotides 596–987 of human MnSOD and nucleotides 537–2218 of human CAT, cloned into the pSP65 vector (Promega, Southamptom, UK). The transcripts were purified on NucTrap columns (Stratagene) and added to the prehybridization solution at 2×10^6 cpm/ml. Hybridization was then carried out at 58.5° C overnight with shaking. After washing with 2× SSC and 0.2× SSC at room temperature and with 0.2× SSC, 0.1% sodium dodecyl sulfate (SDS) at 58.5° C, autoradiography was performed at −80° C with Eastman Kodak (Rochester, NY) BioMax MR film. After autoradiography, the filters were rehybridized with a β-actin control probe transcribed from pTRI-β-actin plasmid (Ambion, Austin, TX). The human MnSOD and CAT cDNAs were kindly provided by Y.-S. Ho (Wayne State University, Detroit, MI).

RESULTS

Normal Lung

No amount of MnSOD protein could be detected immunohistochemically in type II pneumocytes, alveolar macrophages, or bronchial epithelial cells in the controls (Table 3 and Figure 1A). In contrast to MnSOD, catalase stained positively, especially in type II pneumocytes, the staining intensity being intense in one and moderate in four biopsies (Table 3 and Figure 1B). Alveolar macrophages and bronchial epithelial cells were weakly positive for catalase. The staining patterns of MnSOD and catalase were intracytoplasmic and granular, the granularity of catalase being finer. Repeated stainings resulted in good reproducibility.

Northern blotting indicated that both of these enzymes are detectable in BAL fluid samples of healthy lung (Figure 2).

Usual Interstitial Pneumonia and Desquamative Interstitial Pneumonia

The lung biopsies of the patients with UIP and DIP indicated that MnSOD was elevated especially in type II pneumocytes and alveolar macrophages (Table 4 and Figures 3A and 3B). The staining of MnSOD in type II pneumocytes was intense in 3 and moderate in 9 biopsies and that in alveolar macrophages was intense in 4 and moderate in 12 biopsies. The immunoreactivities for catalase were most marked in type II pneumocytes, the immunoreactivities being intense in four and moderate in nine biopsies (Table 4 and Figures 3C–3E). Ciliated columnal epithelial cells showed intracellular positivity for catalase in the apical compartment (Figure 3F), while goblet cells were completely negative for catalase (not shown). The fibromyxoid lesions of UIP, which consisted of fusiformic cells, apparently myofibroblasts and fibroblasts, in a loose fibromyxoid matrix indicating foci of early lesions in UIP, showed positivity for MnSOD and catalase in type II pneumocytes, and showed positivity for catalase in the stromal cells of the fibromyxoid lesions. A few catalase-positive cells were also found around the fibromyxoid lesions. Alveolar and bronchiolar metaplastic epithelium showed positivity for both enzymes, which appeared to be stronger than in normal alveolar and bronchiolar epithelium.

Granulomatous Diseases

We have observed that MnSOD is highly expressed in granulomas and in alveolar macrophages and type II pneumocytes of sarcoidosis and extrinsic allergic alveolitis (3). These experiments were conducted by the avidin–biotin–peroxidase complex method, and the color was developed with diaminobenzidine, which results in a brown color. Therefore, hemosiderin-containing alveolar macrophages may be difficult to distinguish from an immunohistochemical positive reaction. Therefore, the previous findings on MnSOD immunoreactivity were confirmed by a different revealing technique. Reproducibility was confirmed by staining four biopsies of sarcoidosis by the peroxidase-conjugated streptavidin method, using aminoethyl carbazole substrate solution, which results in a red color. These experiments gave results similar to those of our previous findings (only the staining of the granulomas of four biopsies is presented in Table 5).

The lung biopsies of 14 patients with pulmonary sarcoidosis and of 6 patients with extrinsic allergic alveolitis showed posi-

Figure 3. Representative findings of MnSOD and CAT immunoreactivity in usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia (DIP). (*A*) MnSOD is expressed especially in type II pneumocytes of UIP. (*B*) MnSOD stains positively alveolar macrophages (*long arrow*) and type II pneumocytes (*arrowhead*) of DIP. Also, bronchial epithelium stains positively for MnSOD (*short arrow*). (*C*) Positive immunoreactivity for CAT in type II pneumocytes of UIP (*arrow*). (*D*) Negative control with PBS in the alveolar region of DIP. (*E*) CAT is expressed in type II pneumocytes of DIP (*arrows*). (*F*) CAT stains the bronchial epithelium of a patient with DIP. Original magnification: (*A–F*) ×210.

Figure 4. A representative finding of CAT immunoreactivity in sarcoidosis. (*A*) CAT is expressed in the granulomas of sarcoidosis. Notice the negative giant cells and a few intensively stained cells around the granuloma. (*B*) Negative control with PBS in the alveolar region of sarcoidosis. Original magnification: (*A* and *B*) ×210.

tively for catalase in the granulomas of sarcoidosis and extrinsic allergic alveolitis (Table 5 and Figures 4A and 4B). Epithelioid cells showed intense immunoreactivity, whereas Langhans-type giant cells were often negative. Especially type II pneumocytes were positive for catalase, the staining being intense in one biopsy, and moderate in eight biopsies. Positive staining for catalase was also seen in alveolar macrophages and bronchial epithelial cells.

DISCUSSION

This study indicates that the expression of MnSOD is elevated in chronic interstitial pneumonias, UIP and DIP, and in granulomatous diseases, such as sarcoidosis and extrinsic allergic alveolitis, compared with the expression of these enzymes in healthy lung. Manganese SOD is induced especially in type II pneumocytes, alveolar macrophages, and granulomas of diseased lung. In contrast to MnSOD, catalase is also expressed in normal lung, especially in type II pneumocytes, but it is not upregulated in chronic pneumonias or granulomatous diseases of the lung. Compared with MnSOD, catalase is expressed more intensively, especially in the bronchiolar epithelial cells of normal lung.

No previous studies have focused on the localization of MnSOD or catalase in healthy human lung obtained from nonsmokers. We (3) and others (8) showed variable MnSOD reactivity in human lung obtained from patients with an unknown smoking history. The material studied by Coursin and coworkers (8) included four biopsies of patients with lung cancer, and nonmalignant lung showed positive MnSOD reactivity, especially in alveolar macrophages and type II pneumocytes. In our study, weak MnSOD reactivity could also be detected in the same cells of five control subjects with lung cancer and an unknown smoking history (3). We also detected low levels of MnSOD mRNA in the lung homogenates of three nonsmoking adults (27). Furthermore, the present study showed that mRNA of both these enzymes is detectable in the alveolar macrophages of healthy controls. In conclusion, the level of MnSOD is low in healthy lung and is probably induced even in healthy subjects when exposed to exogenous compounds, such as cigarette smoke (28). In addition, it must be noted that MnSOD was not detected by the staining method used, at any of the several dilutions tested. This, however, does not mean that minor amounts of MnSOD protein are not present in the healthy lung.

The present study indicated that catalase is expressed especially in alveolar type II pneumocytes and, to a lesser degree, in the bronchiolar epithelium and alveolar macrophages of healthy lung. This result is in agreement with previous studies on healthy human lung showing that catalase can be detected in alveolar and bronchiolar epithelium (8, 9).

The increased expression of MnSOD in type II pneumocytes and alveolar macrophages is in line with the previous findings on animal models and human lung (3, 6–10). The expression of MnSOD is increased in rat lungs after exposure to hyperoxia (7), and the previous studies have indicated a significant induction of MnSOD, especially in type II pneumocytes (3, 6–10). Manganese SOD is also known to be induced by various cytokines (18, 29), which is in good agreement with the increased expression of MnSOD in smoker's lung and in lungs with sarcoidosis, extrinsic allergic alveolitis, and DIP, and in type II pneumocytes, especially in the fibromyxoid lesions of UIP. Although many of the patients with interstitial lung diseases were smokers, MnSOD was also abundantly expressed in the diseased lung of nonsmoking individuals.

The induction of catalase is controversial. This is the first study on catalase in human lung parenchymal diseases, which shows that catalase is not upregulated in interstitial lung diseases. However, since immunohistochemistry is not precise, minor elevation of catalase in the diseased lung is possible. This result is consistent with many previous studies. Catalase has been shown to be increased by hyperoxia, oxidants, and cytokines in some (17, 30, 31), but not all, investigations (6, 24, 32). Most previous studies have, however, been conducted on animal models or cell cultures. Experiments on human lung have shown that catalase is not elevated by a high oxygen tension in human tracheal epithelial cells during 12 h *in vivo* (23) or during 48 h *in vitro* (24). We investigated the developmental profile of the most important antioxidant enzymes (MnSOD, CuZnSOD, glutathione peroxidase, and catalase) in human lung. The results indicated that catalase was the only antioxidant enzyme that was increased both at the mRNA and at the activity levels during lung morphogenesis toward term (27). Furthermore, previous studies on animal models (20–22) as well as the present study showed remarkable catalase reactivity, especially in alveolar type II pneumocytes, which are the most resistant cell type in the lungs. Thus, these findings suggest that the significance of catalase in pulmonary defense, especially at the alveolar level, is important and has possibly been underestimated.

A combination of MnSOD and catalase has been suggested to play a central role in lung defense against high oxygen tension. This effect has been shown by polyethylene glycol (PEG)-encapsulated SOD and catalase (33). The protection of transgenic mice overexpressing only MnSOD against hyperoxia is minimal or nonexistent, whereas transgenic mice overexpressing superoxide dismutase, catalase, and the cellular glutathione peroxidase show an increased tolerance to hyperoxia (reviewed in Reference 34). The K_m of catalase for H_2O_2 is higher than the K_m of glutathione peroxidase (35), also suggesting the importance of catalase during severe oxidant stress (reviewed in Reference 11). The present study showed that both MnSOD and catalase were expressed most markedly in type II pneumocytes of the patients with UIP and DIP. It should be noted that the expression of these enzymes was most prominent in the well-preserved regions of the lung, but not in the areas of end-stage fibrosis seen in UIP.

In conclusion, the present study showed significant induction of MnSOD and constitutive abundant expression of catalase, especially in the alveolar region of various interstitial lung diseases. The simultaneous expression of both these enzymes may play an important role in the protection of the lung and alveolar type II pneumocytes against the progression of interstitial lung disease.

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